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## T cell recognition of large T and small T antigen in Merkel cell polyomavirus-associated cancer

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Merkel Cell Carcinoma is an aggressive human skin cancer induced by Merkel Cell Polyomavirus (MCPyV). MCPyV is commonly found in human, but the oncogenic transformation takes place during immunosuppression. Two mutation events allow the clonal integration of the viral genome into the host genome and translation of the two viral genes large T (LTA) and small T antigen (STA). Standard treatment with chemotherapy shows poor clinical outcome instead immunotherapy offers new potential treatment strategies. The use of PD-1 checkpoint inhibitors has shown promising results (>50% response rates, RECIST). However, not all patients are able to mount an immune response. Instead adoptive transfer of MCPyV-reactive T cells is an attractive strategy for this cohort.

We have previously identified T cell epitopes from the MCPyV-derived proteins LTA, STA and VP1. Here we aim to expand the knowledge about T cell epitopes by including a broader range of HLA restrictions. We analyzed 31 patients' peripheral blood mononuclear cells through enrichment of low frequency clones, followed by revealing of T cell reactivity using combinatorial color-encoded peptide-MHC multimers. 28 T cell responses against 18 MCPyV-derived peptides were detected. Additional testing has confirmed functional T cell reactivity against one of these epitopes. We analyzed 3 patients' tumor infiltrating lymphocytes by direct *ex-vivo* detection of T cell reactivity using combinatorial color-encoded peptide-MHC multimers. 5 T cell responses against 5 peptides were detected.

The functional T cell response towards detected epitopes is under investigation in order to characterize them as potential T cell targets in a new therapy.

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## Vaccination with proline-substituted neoepitope Trh4 generates enhanced CTL responses against tumors

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Human cancers frequently display defects in their antigen (Ag) processing and presentation pathway that allow for immune evasion, and therefore constitute a significant challenge for T cell-based immunotherapy. T cell epitopes associated with impaired peptide processing (TEIPP) constitute a novel category of immunogenic Ags that are selectively presented on transporter associated with Ag processing-deficient cells. The TEIPP neoepitopes are CD8 T cell targets, derived from non-mutated self-proteins that might be exploited to prevent immune escape. Furthermore, we have previously demonstrated that alteration of cancer epitopes at position 3 to a proline residue in H-2D<sup>b</sup>-binding peptides strongly increases MHC/peptide complex stability and immunogenicity. We have determined the crystal structure of H-2D<sup>b</sup> in complex with the first identified TEIPP Ag (MCLRM TAVM) derived from the Trh4 protein, demonstrating that the peptide induce a non-canonical conformer of His155, known to be important for TCR recognition. Also, we have determined the crystal structure of H-2D<sup>b</sup> in complex with the p3P-modified Thr4 variant since *in vivo* and *in vitro* results demonstrate that vaccination with Thr4-p3P results in significantly enhanced recognition by anti-tumour CTLs. Comparison of structures and functional results provide interesting insights to this epitope.